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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,367	12/27/2002	Rino Rappuoli	PP01651.102; 2302-1651	7808

7590 04/25/2006

Chiron Corporation
P O Box 8097
Emeryville, CA 94662-8097

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,367	RAPPUOLI ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *21-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/27/02* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *020604*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' preliminary amendment filed 11/02/02. With this, Applicants have amended the claims.

Election

2) Acknowledgment is made of Applicants' election filed 02/02/06 in response to the written lack of unity mailed 12/08/05. Applicants have elected invention I, claims 1-20. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)).

Status of Claims

3) Claims 1-34 are pending.

Claims 21-34 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

The elected claims 1-20 are under examination. A First Action on the Merits for these claims is issued.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' information disclosure statement filed 02/06/04. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Priority

5) The instant application is national stage 371 application of PCT/IB00/01440 filed 09/28/00 and claims priority to application 9923060.9 filed 09/29/1999 in United Kingdom.

It is noted that Applicants have submitted a certified copy of the UK priority document.

Specification

6) The instant specification is objected to for the following reason(s):

Figures 1-4, 6, 7 and 9-13 comprise more than one panel(s). Each panel should be further labeled, for example as, Figures 1A, 1B, 1C and 1D. The brief description for these figures provided on pages 5 and 6 of the specification should be amended accordingly to replace, for example, the limitation 'Figure 1' at line 2 of page 5 of the specification with the limitation

Figures 1A-1D--. References to these figures throughout the specification should be amended accordingly.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

7) Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 includes the limitation: '(a) ..... (b) a detoxified *E. coli* LT-K63 and LT-R72 mutant, wherein said vaccine is administered mucosally'. However, there appears to be no descriptive support in the specification, as originally filed, for a mucosal DTPa vaccine comprising the elements recited in part (a) of the claim and both detoxified *E. coli* LT-K63 and LT-R72 mutants, or a double LT mutant having both K63 and R72 as recited, wherein the vaccine containing both said mutant(s) is administered mucosally. Therefore, the above-identified limitation in the claim(s) is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to specific pages and lines providing the descriptive support in the specification as originally filed for the new limitations, or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

8) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

9) Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1, 9, 11 and 19 are vague and indefinite in the use of the abbreviated limitation, 'DTPa', in the claim language. It is suggested that the abbreviation be recited as a full terminology at first occurrence in the base claim, with its abbreviated recitation retained in parentheses.

(b) Claim 1 is vague and confusing in the limitation: '**a** detoxified *E. coli* LT-K63 and LT-R72 mutant' [Emphasis added]. Does it mean that this represents one single mutant with two mutations, one at position 63 and another at position 72?

(c) In claim 15, for clarity and for the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation '(b) is' with the limitation --said detoxified form of cholera toxin or *E. coli* heat labile toxin is .....--.

(d) Claim 15 and claim 1 are inconsistent in scope in the limitation 'LT-K63' and 'LT-R72'. Claim 15 depends from claim 11, part (b) of which recites 'detoxified form of ... cholera toxin'. The dependent claim 15 recites that '(b) is LT-K63 or LT-R72'. Claim 1 however refers to 'LT-K63' and 'LT-R72' as detoxified *E. coli* LT-K63 or LT-R72. Clarification/correction is requested.

(e) Claims 2-10 and claims 12-20, which depend directly or indirectly from claim 1 or claim 11, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 103

10) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

11) Claims 11-16 and 18-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ryan *et al.* (*Immunology Lett.* 69: 59, # 11.19, June 1999 – Applicants' IDS) in view of Marsili *et al.* (EP 0 462 534 A2 – Applicants' IDS).

Ryan *et al.* taught a nasally delivered a pertactin-containing acellular pertussis vaccine combined with a detoxified LTK63 or LTR72 (see abstract).

Ryan *et al.* do not expressly teach that their vaccine comprised a detoxified acellular pertussis holotoxin, detoxified diphtheria antigen or diphtheria toxoid, and a detoxified tetanus antigen or a tetanus toxoid.

However, Marsili *et al.* taught a vaccine comprising an acellular, non-toxic 9K/129G double mutant of pertussis holotoxin, filamentous haemagglutinin (FHA), and the 69 kilodalton protein or pertactin (i.e., additional non-DTP antigen) in combination with diphtheria toxoid and tetanus toxoid (see abstract; claims, especially claim 6; Table on page 14; and Table X). Marsili *et al.* further taught that the non-toxic PT mutant, FHA, and the 69 Kd protein in their vaccine represent antigens of election for developing acellular anti-pertussis trivalent DPT vaccine having the desired features of high immunogenicity and absence of toxicity (see last full paragraph on page 4). Marsili *et al.* additionally taught the drawback of detoxifying a bacterial toxin by chemical detoxification using formaldehyde or glutaraldehyde by stating that such a method leads to reversion to toxicity (see page 2).

Given Marsili's express teaching that the non-toxic PT mutant, FHA, and the 69 Kd protein represent antigens of election for developing acellular anti-pertussis trivalent DPT vaccine having the desired features of high immunogenicity and absence of toxicity, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Ryan's pertactin-containing acellular pertussis vaccine with Marsili's DTPa combination to produce the instant invention with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing a trivalent acellular vaccine that advantageously has the desired features of high immunogenicity and absence of toxicity as taught by Marsili *et al.* in addition to having the ability to confer immunity against diphtheria and tetanus.

Claims 11-16 and 18-20 are *prima facie* obvious over the prior art of record.

12) Claim 17 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Ryan *et al.* (*Immunology Lett.* 69: 59, # 11.19, June 1999 – Applicants' IDS) as modified by Marsili *et al.* (EP 0 462 534 A2 – Applicants' IDS) as applied to claims 16 and 11 above, and further in view of Metcalf (US 5,614,382) and Podda *et al.* (*Ann. Ig.* 3: 79-84, 1991).

The teachings of Ryan *et al.* as modified by Marsili *et al.* are explained above, which do not disclose that the detoxified diphtheria antigen in their vaccine is CRM197.

However, the advantageous substitution of a diphtheria antigen with the non-toxic or detoxified, but immunologically indistinguishable CRM 197 in a vaccine was well known in the art at the time of the instant invention. For instance, Podda *et al.* expressly taught CRM197 to be an ideal candidate to substitute diphtheria toxoid in a vaccine (see summary). Metcalf taught that CRM197 is a non-toxic form of diphtheria toxin which is immunologically indistinguishable from the diphtheria toxin (see first full paragraph under 'Background').

Given Podda's express identification of CRM197 to bean ideal candidate to substitute diphtheria toxoid in a vaccine, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace diphtheria toxoid in Ryan's acellular pertussis vaccine as modified by Marsili's DTPa combination to produce the instant invention with a reasonable expectation of success. Given Metcalf's express teaching that the non-toxic CRM197 is immunologically indistinguishable from the diphtheria toxin, and Marsili's teaching that a chemically detoxified bacterial toxin has the disadvantage of reversion to toxic form, one of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing a diphtheria antigen-containing combination DTPa vaccine that does not have the art-recognized drawback of reversion to toxicity.

Claim 17 is *prima facie* obvious over the prior art of record.

Remarks

13) Claims 1-20 stand rejected.

14) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted to the fax number (571) 273-8300 which receives papers 24 hours a day, seven days a week.

15) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

16) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

April, 2006

S. DEVI, PH.D.
PRIMARY EXAMINER